Remarks/Arguments

Claims 1 and 4 are amended and remain in the application. Claims 2, 3, and 6-28 are cancelled. The amendments to the claims are fully supported by the specification and thus do not constitute new matter.

Rejections under 35 U.S.C. § 102(b)

In the Office Action dated July 1, 2004, the Examiner rejected claims 1-3, 5-7, 12-13, 15-16, and 19-28 as being anticipated by Glueck (XP-00210368) in view of Ramharack (XP-002103071). The claims have been amended so that the phrase "Lp(a) inhibitor" has been replaced by the phrase "retinoid Lp(a) inhibitor". Neither Glueck nor Ramharack disclose the combination of a statin and a retinoid Lp(a) inhibitor. As a result of the amendments to the claims, the basis for the 35 U.S.C. § 102(b) rejection has been rendered moot. Reconsideration and allowance of the amended claims is therefore respectfully requested.

Examiner's Rejections under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-28 as being obvious over Bocan (U.S. Patent No. 6,093,719) in view of Lee (U.S. Patent No. 5,489,611), or in the alternative, over Hirai (U.S. Patent No. 5,260,440) in view of Katocs (U.S. Patent No. 5,219,888). Applicants continue to respectfully traverse this rejection because i) the requirements for a *prima facie* finding of obviousness have not been met; or, in the alternative ii) the invention was otherwise unexpected and thus nonobvious in light of the understanding of the skilled practitioner at the time the invention was made.

A. Requirements for a Finding of Prima Facie Obviousness Not Met

Applicants traverse the Examiner's rejection of claims 1-28 under 35 U.S.C. § 103(a) as being unpatentable over Bocan (U.S. Patent No. 6,093,719) in view of Lee (U.S. Patent No. 5,489,611), or in the alternative, over Hirai (U.S. Patent No. 5,260,440) in view of Katocs (U.S. Patent No. 5,219,888). Applicants respectfully submit that no *prima facie* case of obviousness has been established based on the cited teachings of the prior art.

As a preliminary matter, no one ever combined atorvastatin and a retinoid into a single pharmaceutical composition with a suitable carrier or diluent before Applicants laid claim to such an invention. The Examiner contends, however, that the combination is *prima facie* obvious for

the reasons set forth in the outstanding Office Action. While Applicants appreciate the thoughtful explanations provided by the Examiner, Applicant respectfully traverses this obviousness conclusion and urges reconsideration and withdrawal. When *all* of the relevant art is taken together as a *whole* (as it must be in assessing obviousness), the art actually teaches away from the claimed combination, There is *no teaching or suggestion* in the art that these two particular drugs should be selected from the vast array of available compounds and combined in a single pharmaceutical composition, and there is *no reasonable expectation* of success (i.e., any benefit) taught by the art were that to be done.

At best, the art supports only an "obvious to try" situation. However, for *prima facie* obviousness to exist as provided by MPEP §2142 as relating to the combination of atorvastatin, a retinoid, and a carrier or diluent in a single pharmaceutical composition, there must be a *motivation* for making such a composition. Some reason must exist from the *teachings of the references* (and not via hindsight) to select these specified ingredients and put them together in a single pharmaceutical composition. It is not enough simply to say that there is a general teaching or desire to combine materials (and there is not)—instead, one skilled in the art must be motivated by some teaching in the art to make the specific combination.

And, assuming such motivation (which Applicant submits does not exist here), additionally and separately, the art must teach a reasonable expectation of a successful result. The Examiner has the initial burden to establish both motivation and reasonable expectation. Restated, the law is clear that the Examiner must first establish, *from the art*, the motivation to select the ingredients and establish a reasonable expectation of success. If the rejection does not provide both, Applicants are under no obligation to rebut any presumption, e.g., by providing evidence of an unexpected result. MPEP §2142. This is the law, and it applies whether or not the claims are directed to methods or, as here, to compositions.

1. Applicable Legal Standards

The Federal Circuit has frequently explained what must be shown to establish *prima facie* obviousness, and a brief review of the well-established, directly applicable case law is essential to understand Applicant's position. The specific fact patterns facing the Federal Circuit in the cases discussed below are especially instructive in understanding how the legal standards must

be applied, and these legal standards apply regardless of the statutory class of invention claimed, e.g., composition or method.

In *In re Denzbiczak,* 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999), is a relatively recent case which reversed the Board's holding of obviousness for claims directed to "a large trash bag made of orange plastic decorated with lines and facial features, allowing the bag, when filled with trash or leaves to resemble a Halloween-style pumpkin, or jack-o'-lantern" (at 1615). In reversing the Board's decision, the Federal Circuit explained the analytical framework and burdens necessarily imposed on the Board (and an Examiner) to establish legal "obviousness" under the applicable statute. The Board had found obviousness based on combining three pieces of prior art: (1) conventional trash bags; in view of (2) "Holiday" (a teacher's handbook describing crepe paper Jack-O'-Lanterns stuffed with newspaper); and (3) "Shapiro" (a paper bag pumpkin stuffed with newspaper, painted orange and having black-painted facial features) (at 1616).

The Federal Circuit explained the law of obviousness as applied to these claims and references in the following manner.[1]

> "Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. *** Close adherence to this methodology is especially important in the case of less technologically complex inventions, where the very ease with which the invention can be understood may prompt one 'to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."' (at 1617)

After extensive citations to authority requiring "strict observance" to the requirement that an Examiner "must identify specifically...the reasons [why] one of ordinary skill in the art would have been motivated to select the references and combine them," the Federal Circuit stated *(Id.)*:

> "Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's

[1] The Court supported its discussion of the law by extensive citations to prior decisions which we have omitted from our quotations. Emphasis in all quotations in this Response is supplied by Applicant unless indicated to the contrary.

> disclosure as a blueprint for piecing together the prior art to defeat patentability-the essence of hindsight."

Further explaining the required evidence, the Court said (Id.):

> "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. *** Broad conclusory statements regarding the teaching, of multiple references, standing alone, are not 'evidence.'"

As a basis for reversing the Board, the Federal Circuit held (at 1618):

> "Nowhere does the Board particularly identify any suggestion, teaching, or motivation to combine the children's art references (Holiday and Shapiro) with the conventional trash or lawn bag references, nor does the Board make specific-or even inferential-findings concerning the identification of the relevant art, the level of ordinary skill in the art, the nature of the problem to be solved, or any other factual findings that might serve to support a proper obviousness analysis."

The Dembiczak decision is not the first, or the last, Federal Circuit decision reversing the Board's rejection of claims as obvious in the context of PTO prosecution or addressing the strict requirements and analytical framework essential to assess obviousness. In *In re Geiger,* 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987), the Court addressed the Board's rejection of claims to a method of inhibiting scale formation and corrosion of metal using three ingredients each of which had been separately used for this very same purpose. In reversing the Board, the Court noted (at page 1277-78):

> "Based upon the prior art and the fact that each of the three components of the composition used in the claimed method is conventionally employed in the art for treating cooling water systems, the board held that it would have been prima facie obvious, within the meaning of 35 U.S.C. § 103, to employ these components in combination for their known functions and to optimize the amount of each additive."

The Appellant in Geiger contended that the "PTO has failed to establish a *prima facie* case of obviousness". The Federal Circuit carefully examined the cited prior art cited and agreed, stating (at 1278):

> "At best, in view of these disclosures, one skilled in the art might find it obvious to try various combinations of these known scale

> and corrosion prevention agents. However, this is not the standard of 35 U.S.C. 5 103."

The PTO's failure to establish a *prima facie* case of obviousness (and consequent reversal by the Federal Circuit) was also addressed in *In re Rouoffet, 47* U.S.P.Q.2d 1453 (Fed. Cir. 1998), where the Court noted (at 1455, 1457-58):

> To reject claims in an application under section 103, an examiner must show an unrebutted *prima facie* case of obviousness. *** In the absence of a proper *prima facie* case of obviousness, an Applicant who complies with the other statutory requirements is entitled to a patent.
>
> As this court has stated, "virtually all [inventions] are combinations of old elements." *** ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue.
>
> Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention.
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

The Federal Circuit's admonition that combinations of old elements (i.e., elements *per se* taught in the art even for the same purpose as claimed) can still be patentable was restated in *The Gillette Company v. S. C. Johnson & Son, Inc.,* 15 U.S.P.Q.2d 1923 (Fed. Cir. 1990):

> It is true that [the claimed invention] consists of a combination of old elements so arranged as to perform certain related functions. It is immaterial to the issue, however, that all of the elements were old in other contexts. *What must befound obvious to defeat the patent is the claimed combination.*

And the Court carefully distinguished the legal standard of obviousness from "obvious to try":

> [a]n "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. *** However, we have consistently held that "obvious to try" is not to be equated with obviousness under 35 USC 103.

See also In re Fine, 5 U.S.P.Q.2d 1596, 1598-9 (Fed. Cir. 1988) *(no prima facie* obviousness; "obvious to try" is "not a legitimate test of patentability"); *In re Jones,* 21 U.S.P.Q. 1941 (Fed. Cir. 1992) *(no prima facie* obviousness even though the prior art generically taught Applicants' claimed substituted amine salt of dicamba and the specific salt moiety was known for other acids); *Ecolochem, Inc. v. Southern California Edison* Co., 56 U.S.P.Q.2d 1065, 1072-3 (Fed. Cir. *2000); In re Antonie,* 195 U.S.P.Q. 6 , 8 (CCPA 1977) and *In re Tomlison,* 1 5 0 U.S.P.Q. 623,626 (CCPA 1966).

In these decisions and statements of the applicable law, the Courts make no distinction between composition and method claims. Regardless, the same rules apply with respect to "obvious to try" and *"prima facie* obviousness."

Applicant also respectfully refers the Examiner to MPEP § 2142 regarding obviousness:

1) The concept of *prima facie* obviousness is a "procedural tool of examination" which "allocates who has the burden of going forward with production of evidence in each step of the examination process";
2) The Examiner "bears the initial burden of factually supporting any *prima facie* conclusion of obviousness";
3) If the Examiner "does not produce a *primu facie* case, the Applicant is under no obligation to submit evidence of nonobviousness"; and
4) In determining whether a *prima facie* case of obviousness exists, the Examiner is cautioned that "impermissible hindsight must be avoided and the legal conclusion [of *prima facie* obviousness] must be reached on the basis of the facts gleaned from the prior art".

MPEP § 2142 provides the following guidance regarding what is required before the Examiner can establish *prima facie* obviousness:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure."

See also MPEP § §2143 *et. seq.* and the legal authorities and factual examples there set forth. Again, the MPEP does not distinguish between classes of inventions, and the rules equally apply to compositions and methods.

With these admonitions from the Federal Circuit, the MPEP, as well as the cited supporting case law, Applicants submit that the threshold issue becomes whether the Examiner has carried the burden to establish *prima facie* obviousness from the cited references—is there something in the art that motivates a skilled worker to combine the claimed specific materials into a single pharmaceutical composition coupled with a reasonable expectation that if this were done, a beneficial result would be obtained? For at least the reasons detailed below, Applicant respectfully submits that the answer is "no" as to both issues, and therefore no case of *prima facie* obviousness has been established. Thus, this application should be passed promptly to issue.

2. ***Taken As A Whole, The Prior Art Teaches Away***

As indicated above, the Examiner rejected claims 1-28 as being obvious over Bocan in view of Lee, or in the alternative, over Hirai in view of Katocs. Applicants traverse this rejection, and additionally emphasize that the proper framework for determining *prima facie* obviousness in this case is to consider *all* of the relevant art, both that relied on by the Examiner and that cited by Applicant in the Information Disclosure Statement ("IDS") of record in this application. When all of that art is considered, it is clear that the state of the art as of *Applicant's invention date* (not today) taught away from the claimed invention.

a. ***Bocan in View of Lee***

The Examaner rejected the pending claims based on Bocan in view of Lee. According to the Examiner, Bocan discloses combinations of HMG CoA reductase inhibitors (namely statins) with ACAT inhibitors (Abstract), *but not with Lp(a) inhibitors*. ACAT inhibitors prevent the intestinal absorption of dietary cholesterol into the blood stream or the reabsorption of cholesterol which has been previously released into the intestine through the body's own regulatory action (Bocan, col. 5, lns. 13-16). Lee discloses 9-cis retinoic acid to lower Lp(a), which is a modified form of LDL that is implicated in coronary artery disease (Lee, col. 1, lns. 36-46). According to the Examiner, it would have been obvious to the skilled artisan to further enhance the treatment of coronary artery disease by adding 9-cis retinoic acid to the Bocan composition.

Applicants respectfully submit that Bocan *alone* teaches away from the invention embodied by the pending claims by suggesting or motivating the combination of statins with *other* cholesterol absorption inhibitors, *but not* retinoid Lp(a) inhibitors. Although Lee discloses that Lp(a) is a "modified" form of LDL, *Lp(a) is not LDL*. According to Merriam Webster Online, (http://www.m-w.com/ *last visited September 22, 2004*), the word "modification" is defined in part as the making of a limited change in something or the result of such a change. It goes with out saying that something that has been modified no longer exists in its original form.

Moreover, the Examiner's reasoning would support the notion that HDL, IDL, and VLDL are all "modifications" of LDL. Applicants concede that Lp(a) and LDL (like HDL, IDL, and VLDL) are lipid-protein complexes. A lipoprotein is any of the lipid-protein complexes in which lipids are transported to the blood (http://www.dorlands.com/def.jsp?id=12498320 *last visited October 28, 2003*). Lipoprotein particles consist of a spherical hydrophobic core of triglycerides or cholesteryl esters surrounded by an amphipathic monolayer of phospholipids, cholesterol, and apolipoproteins.

Like LDL, Lp(a) contains cholesterol, phospholipids, cholesterol esters, triglycerides, and apolipoprotein B (apo-B). However, Lp(a) has a different *structure* and *function* than LDL. Indeed, Lp(a) has been characterized as a "recalcitrant, unruly step-child in the family of lipoproteins".[2] Although Lp(a)'s protein and lipid composition closely resemble LDL, *the distribution of its plasma levels and its metabolism are distinctive*. As depicted in the Table below, Lp(a) contains apolipoprotein(a) (apo(a)), which is among the most polymorphic proteins

[2] "Lipoprotein(a): intrigues and insights", H. Hobbs, *et. al.*, Curr. Op. Lip. 10(3) 225-236 (June 1999).

in man. Apo(a) is a glycated protein that is attached to apo-B via a disulfide bridge. Apo(a) is a highly glycosylated, plasminogen-resembling protein that varies in size from approximately 300-800 kDa. Plasma levels of Lp(a) vary over a 1000-fold range (from 0.1 to over 100 mg/dl) and have a highly skewed distribution. Lp(a) remains the focus of medical interest because high circulating levels are associated with accelerated atherosclerosis.

Common Plasma Lipoprotein Classes

CLASS	APOLIPOPROTEINS	OTHER COMPONENTS
LDL	B-100	Cholesterol Phospholipids Cholesterol esters Triglycerides
Lp(a)	B-100, a	Cholesterol Phospholipids Cholesterol esters Triglycerides

There is no figurative "LDL lynchpin" that connects Bocan to Lee. Since LDL and Lp(a) are not the same entities, there is no basis for combining the references. Therefore, Bocan in view of Lee fails to provide a motivation to the skilled practitioner to investigate an atorvastatin/retinod Lp(a) inhibitor combination. The art available to the skilled practitioner taken in its totality fail to meet the first and second requirements of the *prima facie case* and moreover, teaches away from a statin/retinoid combination.

Indeed, the references *teach away* from the claimed invention, by instead motivating the skilled artisan to investigate, *at most*, a ternary combination of an LDL inhibitor, ACAT inhibitor, and Lp(a) inhibitor, *not a binary combination consisting of a statin and a retinoid Lp(a) inhibitor* (as recited in amended claim 1, *infra*). Moreover, at the time of the invention, combining a statin with a retinoid Lp(a) inhibitor was not an obvious thing to do. Although some pharmacological agents had been reported to modulate Lp(a) (including nicotinic acid,[3] gemfibrozil[4], as well as the retinoids disclosed by Lee), the effect of statins on Lp(a) provided what can best be said as

[3] *See* Hobbs, ref. 2.

[4] "Gemfibrozil significantly lowers cynomolgus monkey plasma lipoprotein(a) –protein and liver apolipoprotein(a) mRNA levels", R. Ramharack *et. al.*, J. Lip. Res., 36, 1294-1304 (1995).

contradictory findings. In most cases, no significant effect was reported.[5,6,7,8,9] In other studies, a statin-mediated *increase* in Lp(a) was observed.[10,11,12,13] Therefore, the art teachings and the state of understanding of skilled practitioners as of the filing date of the application teach away from a combination comprising a statin and a retinoid, or that such a combination would successfully lower Lp(a) more than a retinoid such as 9-cis retinoid acid used alone.

As a result, the Examiner has not established the *prima facie* obviousness of the invention in light of the Bocan and Lee.

b. Hirai in View of Katocs

Hirai discloses that HMG CoA reductase inhibitors (particularly pravastatin) are useful in treating atheroscleosis. However, Hirai does not disclose, suggest, or otherwise provide motivation to combine atorvastatin with an Lp(a) inhibitor, namely, atorvastatin with a retinoid. Katocs discloses the therapeutic use of retinoids to *increase HDL levels* for the treatment and prevention of coronary artery disease and to protect against atherosclerosis (col. 2, lines 22-25). *Katocs does not, however, disclose the use of retinoids to lower Lp(a) levels.* Furthermore, Katocs does not disclose, suggest, or otherwise provide motivation to combine atorvastatin with a retinoid LP(a) inhibitor, namely, a stain with a retinoid.

Because Hirai and Katocs, taken alone or in combination, fail to disclose the combination of a statin and LP(a) inhibitor, let alone the use of retinoids as Lp(a) inhibitors, the references fail

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[5] "Serum Lp(a) concentrations are unaffected by treatment with HMG-CoA reductase inhibitor pravastatin: result of a 2-year investigation", H. Fiesler *et. al.*, Clin. Chim. Acta, 204, 291-300 (1991)

[6] "Effects of simvastatin on lipoprotein(a)and lipoprotein composition in patients with nephrotic syndrome", C. Wanner *et. al.*, Clin. Nephrol. 41, 138-143 (1994).

[7] "Effect of pravastatin on serum lipids, apolipoprotein and lipoprotei(a) in patients with non-insulin dependent diabetes mellitus", F. Umeda *et. al.*, Endocrin. Japan, 39, 45-50 (1992).

[8] "Effects of one year of treatment with pravastatin, an HMG-CoA reductase inhibitor, on lipoprotein-a", D. Hunninghake *et. al.*, J. Clin. Pharmacol., 33, 574-580 (1994).

[9] "Group TSPS. Comparison of the efficacy, safety, and tolerability of simvastatin and pravastatin fir hypercholesterolemia", The Simvastatin Pravastatin Study Group, Am. J. Cardiol., 71, 1408-1414 (1993).

[10] "Genetic determinants of responsiveness to the HMG-CoA reducatase inhibitor fluvastatin in patients with molecularly defined heterozygous familial hypercholesterolemia", E. Leitersdorf *et. al.*, Circulation, 87, 35-44 (1993).

[11] "A randomized trial of the effects of atorvastatin and niacin in patients with combined lipidemia or hypertriglyceridemia", J. McKenny *et. al.*, Am. J. Med., 104, 137-143 (1998)

[12] "Behavior of Lp(a) and apolipoproteins (A1, B, C2, C3, E) during and after therpy with simvastatin", T. Sampietro *et. al.*, Cardiovasc. Drug Therapy, 9, 785-789 (1995).

[13] "Apolipoprotei(a) polymorphism predicts theincrease of Lp(a) by prevastatin in patients with familial hypercholesterolemia treated with bile acid sequestration", I. Klausen *et. al.*, Eur. J. Clin.. Invest., 23, 240-245 (1993).

to suggest or motivate the skilled artisan to combine an Lp(a) inhibitor with a statin. Moreover, as with Bocan and Lee, Hirai and Katocs, taken separately or in combination, fail to provide a reasonable expectation that such a combination would succeed as a treatment for vascular disorders. Finally, Hirai and Katocs, taken alone or in combination, fail to teach or suggest all the limitations claimed by the instant application.

As a result, the Examiner has not established the *prima facie* obviousness of the invention in light of the Hirai and Katocs.

3. ***Notwithstanding Cited References, Invention is Unexpected and thus Nonobvious***

In the alternative, Applicants assert their invention is nonobvious in light of the understanding of the skilled practitioner at the time the invention was made. As is understood from the previous paragraphs, Applicants' invention is directed to a pharmaceutical combination comprising a statin (particularly atorvastatin) and a retinoid (particularly 9-cis-retinoic acid, 13-cis-retinoic acid, trans-retinal, trans-retinol, 13-cis-retinol, 13-cis-retinal, 9-cis-retinol, or 9-cis-retinal) that can be used to treat vascular diseases associated with high LDL and/or Lp(a) levels. Moreover, as indicated previously, although Lp(a)'s protein and lipid composition closely resemble LDL, it differs in the presence of apo(a). Moreover, the distribution of Lp(a) plasma levels and metabolism are distinctive from LDL.

As indicated earlier, some pharmacological agents had been reported to modulate Lp(a) at the time of the invention.[14] However, although the LDL lowering effect of statins had been well documented, the effect of statins on Lp(a) provided no significant effect or statin-mediated *increases* in Lp(a) concetrations.[15] Therefore, given the state of understanding of skilled practitioners as of the filing date of the application, a combination comprising a statin and a retinoid would at best be expected to provide merely additive results with respect to lowering Lp(a) (no effect from statin, lowering effect from retinoid), and at worst, an Lp(a) elevating effect (elevating effect of statin greater than lowering effect of retinoid).[16]

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[14] *See* refs. 2 and 3.
[15] *See* refs. 4-13.
[16] As indicated, the most that can be said of that the art, taken as a whole, teaches away from a statin/retinoid combination, and that such a combination would not be considered to successfully lower Lp(a).

However, several research groups have recently reported the unforeseen ability of statins to lower Lp(a). For example, Gonbert and coworkers evaluated the impact of statin therapy on plasma levels of Lp(a) over six weeks.[17] In patients treated with either simvastatin or atorvastatin they found that atorvastatin moderately but significantly lowered Lp(a) levels after six weeks, whereas simvastatin treatment resulted in minor reduction. Similarly, Van Wissen and coworkers evaluated the effect of statins on Lp(a) concentrations in a patient population having heterozygous familial hypercholesterolemia.[18] Familial hypercholesterolemia (FH) not only have a two- to three-fold increase in plasma LDL concentrations, they also have Lp(a) levels that are twice as high as normal. After two years of treatment with simvastatin or atorvastatin, a study population of patients with FH had significantly lower levels of Lp(a) compared to baseline. Finally, Schaefer and coworkers observed that when dosed at 40 mg daily atorvastatin significantly reduced Lp(a) concentration in patients with coronary heart disease versus control subjects.[19]

Taken together, the results of Gonbert, Van Wissen, and Schaefer suggest that at the time of the invention, the combination of a statin with an Lp(a) inhibitor *would have provided an unexpected result with respect to lowering Lp(a) levels.* Gonbert and Van Wissen support the conclusion that the combination of atorvastatin and a retinoid would have provided a greater than additive reduction in Lp(a) concentration. Based on this assertion alone, the combination meets the patentability requirements as codified at 35 U.S.C § 103.

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[17] "Atorvastatin lowers lipoprotein(a) but not apolipoprotein(a) fragment levelsin hypercholesterolemic subjects at high cardiovascular risk", S. Gonbert *et. al.*, Atherosclerosis, 164, 305-311 (2002).

[18] "Long term statin treatment reduces lipoprotein (a) concentrations in heterozygous familial hypercholesterolemia", S. Van Wissen, Heart, 89, 893-896 (2003).

[19] "Comparisons of effects of statins (atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) on fasting and postprandial lipoproteins in patients with coronary heart disease versus control subjects", E. Schaefer *et. al.*, Am. J. Cardiol., 93, 31-39 (2004).

Conclusion

Reconsideration and allowance of the claims is respectfully requested. The Examiner is invited to contact the Applicant's attorney at the telephone number provided below to discuss any questions or aspects of the present case.

Respectfully submitted,

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